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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate) capsule for oral use
Initial U.S. Approval: [year]

----------------------------INDICATIONS AND USAGE---------------------------
PRADAXA is a direct thrombin inhibitor indicated for

- the prevention of stroke and systemic embolism in patients with atrial fibrillation (1.1)
- the reduction of vascular mortality in patients with atrial fibrillation (1.2)

----------------------DOSAGE AND ADMINISTRATION-----------------------
- Do not open the capsules and do not swallow the pellets outside the capsules (2)
- Recommended Dose: 150 mg taken orally, twice daily (2.1, 2.2)
- In high bleeding risk patients, consider 110 mg taken orally, twice daily (2.3)
- Discontinue Vitamin K antagonists before using dabigatran (2.4)
- Switching from or to parenteral anticoagulants requires specific timing (2.5)
- Take a missed dose as soon as possible on the same day if 6 hours prior to next scheduled dose. Do not double the daily dose. (2.6)
- Surgical interventions may require the temporary discontinuation of dabigatran (2.7)
- Patients can stay on dabigatran while being cardioverted (2.8)

---------------------DOSAGE FORMS AND STRENGTHS----------------------
Capsules 110 mg, 150 mg (3)

-------------------------------CONTRAINDICATIONS------------------------------
- Active major bleeding or medical conditions associated with an increased risk of bleeding (4.1)
- Severe renal impairment (CrCl <30 mL/min) (4.2)
- Concomitant treatment with systemic ketoconazole (4.3)
- Placement of indwelling spinal or epidural catheter or port and within first hour after removal (4.4)
- Hypersensitivity to dabigatran etexilate (4.5)

-----------------------WARNINGS AND PRECAUTIONS------------------------
- General risk of bleeding (5.1)
- Use caution in conditions with increased risk of hemorrhage (5.2)
- Use caution with P-gp inducers (5.3)

------------------------------ADVERSE REACTIONS-------------------------------
Most common adverse reactions are: bleeding, including life-threatening and fatal bleeding, and dyspepsia or dyspepsia like symptoms (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***.**

------------------------------DRUG INTERACTIONS-------------------------------
~~1~~• Concomitant treatment with systemic ketoconazole (4.3, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of Stroke and Systemic Embolism

PRADAXA is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

1.2 Reduction of Vascular Mortality

PRADAXA is indicated for the reduction of vascular mortality in patients with atrial fibrillation.

2 DOSAGE AND ADMINISTRATION

Do not open the capsules and do not swallow the pellets outside the capsule. PRADAXA may be administered with or without food *[see Clinical Pharmacology (12.3)]*.

2.1 Prevention of Stroke and Systemic Embolism

The recommended dosage of PRADAXA is 150 mg taken orally, twice daily.

2.2 Reduction of Vascular Mortality

The recommended dosage of PRADAXA is 150 mg taken orally, twice daily.

2.3 High Bleeding Risk Patients

For those patients with a potentially higher risk of bleeding a PRADAXA dose of 110 mg taken orally, twice daily may be considered *[see Use in Specific Populations (8.7)]*.

2.4 Switching from Vitamin K Antagonist

In patients currently taking a Vitamin K antagonist, PRADAXA should only be started after Vitamin K antagonists have been discontinued and their INR is below 2.0.

2.5 Switching from or to Parenteral Anticoagulants

In patients currently taking a parenteral anticoagulant, PRADAXA should be given 0 to 2 hours prior to the time that the next dose of the alternate therapy would be due or at the time of discontinuation in case of continuous treatment (e.g., intravenous UFH). In patients currently taking PRADAXA, wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

2.6 Missed Dose

If the prescribed dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A dose may be taken up to 6 hours prior to the next scheduled dose. A missed dose should be omitted if it cannot be taken more than 6 hours before the next scheduled dose. The patient should not take the missed dose by doubling the daily dose to make up for missed doses.

2.7 Surgery and Interventions

Patients on PRADAXA who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of PRADAXA.

Preoperative Phase

In advance of invasive or surgical procedures, PRADAXA should be stopped temporarily because of an increased risk of bleeding. If possible, PRADAXA should be discontinued at least 24 hours before invasive or surgical procedures. In high bleeding risk patients *[see Use in Specific Populations (8.7)]* or in major surgery in which complete hemostasis may be required consider stopping PRADAXA 2 to 4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer and this should be considered in advance of any procedures *[see Use in Specific Populations (8.6)]*.

PRADAXA is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then PRADAXA should be stopped at least 5 days before major surgery.

If an acute intervention is required, PRADAXA should be temporarily discontinued. A surgery/intervention should be delayed, if possible, until at least 12 hours after the last dose is taken. If surgery cannot be delayed, there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture

Procedures such as spinal anesthesia may require complete hemostasis function.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of PRADAXA. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period

Resume treatment as soon as complete hemostasis is achieved.

2.8 Cardioversion

Patients can stay on PRADAXA while being cardioverted *[see Use in Specific Populations (8.8)]*.

3 DOSAGE FORMS AND STRENGTHS

110 mg: A capsule with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted in black with “R110”.

150 mg: A capsule with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted in black with “R150”.

4 CONTRAINDICATIONS

4.1 Active Bleeding

PRADAXA is contraindicated in patients with active bleeding or medical conditions associated with an increased risk of bleeding *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.2 Severe Renal Impairment
PRADAXA is contraindicated in patients with severe renal impairment (CrCl <30 mL/min).

4.3 Concomitant Treatment
PRADAXA is contraindicated in patients being treated concomitantly with systemic ketoconazole.

4.4 Spinal Catheter
PRADAXA use in patients undergoing spinal/epidural anesthesia or spinal puncture increases the risk of bleeding. PRADAXA is contraindicated during the placement of a spinal or epidural catheter or port and within the first hour following removal.

4.5 Hypersensitivity
PRADAXA is contraindicated in patients with known hypersensitivity to dabigatran etexilate (e.g., urticaria, bronchospasm, rash, and pruritus) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding
Major or severe bleeding may occur at any site and regardless of location may lead to disabling, life-threatening or fatal outcomes. An unexplained drop in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with PRADAXA. In patients who are bleeding, the aPTT test maybe useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity to dabigatran etexilate. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

5.2 Increased Risk of Hemorrhage
As an anticoagulant, PRADAXA capsules should be used with caution in conditions with an increased risk of bleeding. Co-administration of anti-platelet (including aspirin and clopidogrel) and NSAID therapies is known to increase the risk of bleeding *[see Adverse Reactions (6)]*.

The following treatments have not been studied in this patient population and may increase the risk of bleeding when used concomitantly with PRADAXA capsules: warfarin or vitamin K antagonists, unfractionated heparins (except at doses necessary to maintain a patent central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, prasugrel; and the P-gp inhibitors itraconazole, tacrolimus, cyclosporine; and ritonavir, nelfinavir, saquinavir and tipranavir.

5.3 Interaction with P-gp Inducers
The concomitant use of PRADAXA with strong P-gp inducers (e.g., rifampicin, carbamazepine, or St. John's Wort) may lead to reduced dabigatran plasma concentrations. Strong P-gp inducers should be co-administered with caution *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are also discussed elsewhere in the labeling:

- Bleeding and bleeding related events (e.g., anemia, thrombocytopenia) may be caused by PRADAXA, as a consequence of its anticoagulant effect. Major or severe bleeding may occur and regardless of location may lead to disabling, life-threatening or fatal outcomes *[see Warnings and Precautions (5.1)]*.
- Bleeding incidence was increased approximately 2-fold during concomitant aspirin or clopidogrel use or the combination, and by approximately 50% with concomitant NSAID use in treatment groups *[see Warnings and Precautions (5.2)]*.
- Hypersensitivity *[see Contraindications (4.5)]*.

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience
Two doses (110 mg and 150 mg BID) of PRADAXA were compared with open-label warfarin in the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy), the Phase III trial in the prevention of thromboembolic stroke and systemic embolism in more than 18,000 atrial fibrillation patients with a median duration of 20 months *[see Clinical Studies (14)]*.

Drug Discontinuation
Over the course of the trial, the total rate of patients with adverse events leading to treatment discontinuation was 19% for PRADAXA 110 mg, 20.5% for PRADAXA 150 mg and 15.7% for warfarin. The most frequent adverse events for PRADAXA leading to discontinuation were gastrointestinal events.

Bleeding Definitions
In the RE-LY study, bleeding was classified as major according to the following guidelines.

Major bleeding fulfilled one or more of the following criteria:
1. Bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells.
2. Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:
1. Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per liter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Bleeding
Table 1 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RE-LY study, with the annualized bleeding rate in (%). Both PRADAXA doses were associated with a lower yearly event rate for major bleeds, minor bleeds and any bleeds as compared with warfarin treatment. Subjects randomized to PRADAXA 110 mg BID had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.80 [p=0.0026]). In Table 1, the

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category of major bleeds includes both life-threatening and non-life-threatening bleeds. Intracranial bleeds are a sub-category of life-threatening bleeds. Intracranial bleeds include intracerebral (hemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 1 Frequency and Annualized Event Rate (%) of Major and Other Bleeding Events

	PRADAXA 110 mg BID N (%)	**PRADAXA 150 mg BID N (%)**	**Warfarin N (%)**
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds*	342 (2.87)	399 (3.32)	421 (3.57)
Hazard ratio vs warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Hazard ratio vs warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
ICH	27 (0.23)	38 (0.32)	90 (0.76)
Hazard ratio vs warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	<0.0001	<0.0001	
Any bleeds[a]	1754 (14.74)	1993 (16.56)	2166 (18.37)
Hazard ratio vs warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	<0.0001	0.0016	

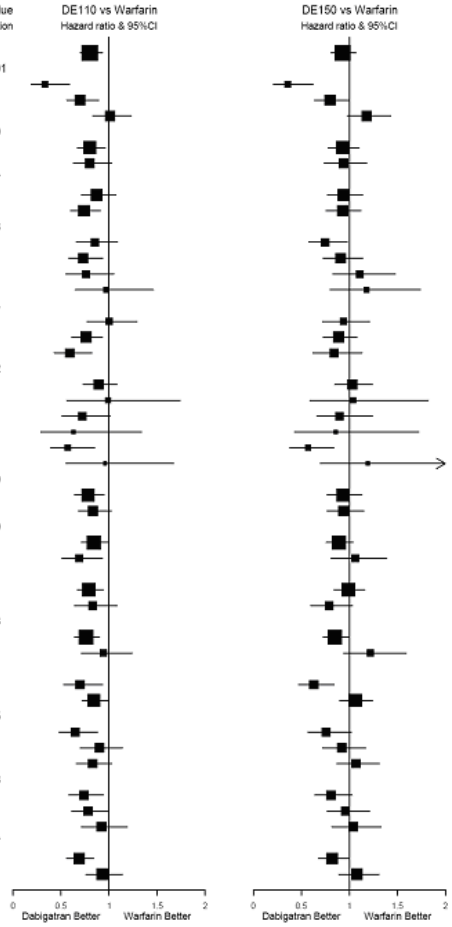
*Adjudicated Bleeds
ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.
[a] Investigator-reported bleeding events

PRADAXA treatment resulted in a higher incidence of major gastrointestinal bleeds (1.14% 110 mg, 1.57% 150 mg; 1.07% warfarin) and any gastrointestinal bleeds (5.41% 110 mg, 6.13% 150 mg, and 4.02% warfarin) compared to warfarin.

The risk of major bleeding with PRADAXA110 mg and 150 mg was consistent across all major subgroups of baseline characteristics (Figure 1) with the exception of age. There was a higher risk of bleeding with PRADAXA 150 mg in patients ≥75 years of age.

Figure 1: Baseline characteristics across subgroups for major bleeds by dose

Subgroup	Patients Total no.	DE110 % per year	DE150 % per year	Warfarin % per year	P−value Interaction
All patients	18113	2.87	3.32	3.57	
Age (years)					<0.0001
<65	2981	0.81	0.88	2.43	
65<= and <75	7894	2.29	2.60	3.24	
>=75	7238	4.44	5.12	4.39	
Gender					1.00
Male	11514	2.92	3.37	3.63	
Female	6598	2.79	3.23	3.46	
VKA use at entry					0.47
Naive	9126	3.11	3.33	3.57	
Experienced	8984	2.66	3.30	3.57	
BMI (kg/m2)					0.18
<25	4697	3.77	3.33	4.42	
25<= and <30	7111	2.50	3.10	3.39	
30<= and <35	4038	2.45	3.52	3.22	
>=35	2241	3.03	3.66	3.12	
CrCL (mL/min)					0.34
30<= and <50	3343	5.65	5.27	5.68	
50<= and <80	8297	2.87	3.34	3.78	
>=80	5658	1.48	2.09	2.49	
Region					0.42
USA, Canada	6533	4.19	4.81	4.72	
Central Europe	2119	1.74	1.84	1.77	
Western Europe	4651	1.87	2.33	2.59	
Latin America	956	2.01	2.72	3.18	
Asia	2782	2.22	2.17	3.82	
Other	1072	3.60	4.42	3.79	
ASA use at baseline					0.90
No	10960	2.41	2.87	3.07	
Yes	7153	3.61	4.06	4.35	
Stroke/SEE/TIA					0.09
No	14159	2.91	3.06	3.45	
Yes	3953	2.76	4.20	4.00	
Heart Failure					0.21
No	13203	2.73	3.38	3.45	
Yes	4904	3.26	3.10	3.90	
Diabetes and age>=65					0.08
No	14616	2.57	2.87	3.36	
Yes	3496	4.14	5.34	4.41	
Hypertension and age>=65					0.01
No	5922	2.13	1.90	3.01	
Yes	12190	3.24	4.02	3.84	
CHADS2 score					0.35
1	5331	1.88	2.20	2.90	
2	6453	2.98	3.04	3.31	
3+	5876	3.80	4.86	4.61	
AF type					0.58
Persistent	5789	2.87	3.14	3.88	
Paroxysmal	5943	3.05	3.74	3.91	
Permanent	6375	2.74	3.07	2.96	
Centre INR % time in range 2−3					0.07
<67%	9073	2.69	3.16	3.87	
>=67%	8951	3.02	3.49	3.25	



Allergic reactions or drug hypersensitivity including urticaria, bronchospasm, rash and pruritus have been reported in patients who received PRADAXA.

Gastrointestinal (GI)/Dyspepsia
PRADAXA subjects had an increased incidence of GI adverse events (AEs) (34.6%, 34.5%, and 24.1% for PRADAXA 110 mg, PRADAXA 150 mg, and warfarin, respectively). Additional GI events that were reported more frequently with PRADAXA treatment included upper abdominal pain, gastritis, abdominal discomfort, gastroesophageal reflux disease, dysphagia, and flatulence (Table 2). There was no consistent dose-response relationship with respect to GI AEs.

Table 2 Number (%) of Subjects with Dyspepsia and Gastritis-like Symptoms (Safety Set)

	PRADAXA 110 mg BID N (%)	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Number of subjects	5983	6059	5998
Total with dyspepsia/gastritis	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia*	761 (12.7)	738 (12.2)	354 (5.9)
Gastritis-like symptoms[a**]	297 (5.0)	257 (4.2)	142 (2.4)

Percentages were calculated using total number of subjects per treatment as the denominator.
*Dyspepsia includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort.
**Gastritis-like includes gastritis, GERD, esophagitis, gastritis erosive, gastric hemorrhage, gastritis hemorrhagic, hemorrhagic erosive gastritis.
[a] Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reporting the same subject.

Liver Function Tests
In the RE-LY study, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in PRADAXA vs warfarin treated patients (Table 3).

Table 3 Summary of Abnormal Liver Function Tests, Number (%) of Subjects (Safety Set)

LFT elevation	PRADAXA 110 mg BID N (%)	PRADAXA 150 mg BID N (%)	Warfarin N (%)
Total treated	5983	6059	5998
ALT or AST >3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST >5xULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT or AST >3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.

Overview of Adverse Events from RE-LY
The incidence of AEs was similar between subjects treated with PRADAXA 110 mg BID and PRADAXA 150 mg BID (78.6% and 78.3%, respectively) vs 75.9% of subjects treated with warfarin. The incidence of serious adverse events was similar across treatment groups. However, PRADAXA subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalization as compared to warfarin subjects.

Adverse events classified by system organ class and preferred terms reported ≥5% from any treatment group of the RE-LY study are shown in Table 4 below. The observed incidences of adverse events for PRADAXA were in the range of warfarin. Diarrhea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with PRADAXA110 mg and PRADAXA 150 mg treatment, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for PRADAXA 110 mg, PRADAXA 150 mg, and warfarin, respectively).

Table 4 Adverse Events Reported in at Least 5.0% of Subjects in PRADAXA Arms (Safety Set)

System Organ Class/ Preferred term	PRADAXA110 mg BID N (%)	PRADAXA150 mg BID N (%)	Warfarin N (%)
Dyspnea	498 (8.3)	526 (8.7)	551 (9.2)
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Edema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Diarrhea	355 (5.9)	367 (6.1)	328 (5.5)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)

Percentages were calculated using total number of subjects per treatment as the denominator.

7 DRUG INTERACTIONS

See Clinical Pharmacology (12.3)

Ketoconazole

Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple dosing of 400 mg ketoconazole QD. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole *[see Contraindications (4.3) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. PRADAXA has been shown to decrease the number of implantations in rats when given at doses of 200 mg/kg. PRADAXA should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

Safety and effectiveness of PRADAXA during labor and delivery have not been established.

8.3 Nursing Mothers

It is not known whether PRADAXA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRADAXA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients has not been established.

8.5 Geriatric Use

Of the total number of subjects in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of bleeding increased with advancing age in all treatment groups. The relative risk of bleeding for PRADAXA 150 mg BID vs warfarin increased in patients ≥75 years of age. PRADAXA is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal Impairment

The AUC of dabigatran after the oral administration of dabigatran etexilate is approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCl between 30 to 50 mL/min) than in those without renal insufficiency. In a small number of volunteers with severe renal insufficiency (CrCl <30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than observed in a population without renal insufficiency *[see Contraindications (4.2)* and *Clinical Pharmacology (12.3)]*.

Table 5 Half-life of Total Dabigatran in Healthy Subjects and Subjects with Impaired Renal Function

Glomerular filtration rate (CrCl) [mL/min]	Median half-life (gCV%; range) [h]
>80	13 (26%; 11-22)
>50 - ≤80	15 (43%; 12-34)
>30 - ≤50	18 (19%; 13-23)
≤30	27 (15%; 22-35)

8.7 High Bleeding Risk Patients

For those patients with a potentially higher risk of bleeding, (e.g., age ≥75 years, $CHADS_2$ score of ≥3, moderate renal impairment (30 to 50 mL CrCL/min), concomitant treatment with P-gp inhibitors, or previous gastrointestinal bleed), a reduced dose of 110 mg twice daily may be considered *[see Dosage and Administration (2.3)]*.

8.8 Cardioversion

A total of 1255 subjects had cardioversions performed during the RE-LY study, 409 (6.8%), 415 (6.8%) and 431 (7.2%) in the PRADAXA 110 mg, PRADAXA 150 mg and warfarin treatment groups respectively. The rate of stroke occurring within 30 days of cardioversion was low and similar across all treatment groups [PRADAXA 110 mg (0.03%), PRADAXA 150 mg (0.03%) and warfarin (0.02%)].

8.9 Hepatic Insufficiency

Hepatic patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥2 ULN, or hepatitis A, B or C were excluded in clinical trials.

8.10 Body Weight

The dabigatran trough concentrations were approximately 20% lower in patients with a BW of >100 kg compared with those with a BW of 50 to 100 kg. The majority (80.8%) of the subjects were in the BW of ≥50 kg and <100kg category with no clear difference detected. Limited data in patients with a BW of ≤50 kg are available.

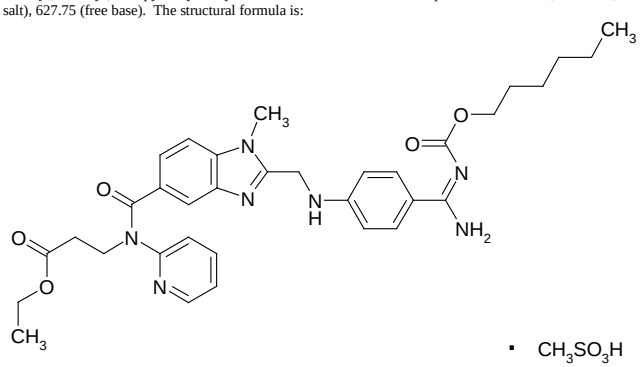
10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or dabigatran. In the event of hemorrhagic complications appropriate clinical support should be initiated, treatment with PRADAXA must be discontinued and the source of bleeding investigated. Dabigatran is primarily excreted in the urine therefore adequate diuresis must be maintained. Surgical hemostasis or the transfusion of fresh frozen plasma or RBCs may be considered. While dabigatran can be dialyzed (protein binding is low), there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment can be given.

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate is: β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino] iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

Each capsule for oral administration contains 126.83 mg or 172.95 mg dabigatran etexilate mesylate (as salt), which is equivalent to 110 mg or 150 mg, respectively, of free base and the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shells are composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabigatran etexilate is a pro-drug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, direct thrombin inhibitor and is the main active component in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits both free and clot-bound thrombin, and thrombin-induced platelet aggregation.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the aPTT. With an oral dose of 150 mg BID the median peak aPTT is approximately 2x control. Twelve hours after the last dose the median aPTT is 1.5x control, with less than 10% of patients exceeding 2x control. The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients on dabigatran etexilate. In transition of dabigatran etexilate to warfarin therapy, the INR is unlikely to be interpretable.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 3 to 7%. After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with C_{max} attained

within 0.5 and 2.0 hours post administration. Co-administration of dabigatran etexilate with a high-fat meal delayed the time to peak plasma concentration by approximately 2 hours but had no effect on the bioavailability of dabigatran etexilate; dabigatran etexilate may be administered with or without food.

A study evaluating post-operative absorption of dabigatran etexilate, 1 to 3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a flat plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a post-operative period because of contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

The oral bioavailability of dabigatran etexilate may be increased by 75% compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. The integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate.

Distribution
Low (34% to 35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60 to 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran. C_{max} and the area under the plasma concentration-time curve were dose proportional.

Elimination
After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Fecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 to 94% of the administered dose by 168 hours post dose. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

The half-life is 10.7 h and 11.2 h in healthy elderly (≥65 years) male and female volunteers, respectively. The half-life is prolonged to 15.3 h and 18.4 h in patients with mild or moderate renal impairment, respectively.

Metabolism
After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acyl-glucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods.

Drug Interactions
In vitro assessment of drug interactions
Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and had no effects *in vitro* on human cytochrome P450 enzymes. Therefore interactions with other drugs that utilize these pathways are unlikely.

In vivo assessment of drug interactions
In clinical studies exploring CYP3A4, CYP2C9, and P-gp pathways, dabigatran etexilate did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, diclofenac, digoxin, pantoprazole, and ranitidine.

In the RE-LY study, dabigatran plasma samples were also collected. Trough plasma concentrations with the concomitant use of PPIs, amiodarone, verapamil, digoxin and H2 antagonists did not appreciably change the concentration of dabigatran and were not associated with any increased risk of bleeding.

The following are listed for reference with dabigatran etexilate:

Ketoconazole:
Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple dosing of 400 mg ketoconazole QD. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole *[see Contraindications (4.3) and Drug Interactions (7)]*.

Verapamil:
When dabigatran etexilate was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

Immediate-release verapamil: single dose 120 mg administered one hour prior to dabigatran etexilate intake increased dabigatran AUC by 143% and C_{max} by 179%.

Extended-release verapamil: single dose 240 mg administered concurrently with dabigatran etexilate intake increased dabigatran AUC by 71% and C_{max} by 91%.

Multiple doses of immediate-release verapamil: 120 mg BID for 3 days, with the last dose given 1 hour before a single dabigatran etexilate dose of 150 mg elevated dabigatran AUC by 54% and C_{max} by 63%. An increased dose of verapamil, 120 mg QID, with the last morning dose also given 1 hour before dabigatran etexilate, elevated dabigatran AUC by 43% and C_{max} by 38%. When the treatment sequence was changed and verapamil was given 2 hours after dabigatran etexilate, the dabigatran AUC and C_{max} increased 18% and 12% respectively. In addition, dabigatran plasma samples were also collected in the RE-LY study *[see Clinical Studies (14)]*. Trough plasma concentrations were approximately 16.1% higher but were not associated with any increased risk of bleeding compared with the combination of warfarin and verapamil.

Amiodarone:
When dabigatran etexilate was co-administered with a single 600 mg oral dose of amiodarone, the dabigatran AUC and C_{max} increased by 58% and 50%, respectively. In addition, plasma samples were also collected in the RE-LY study *[see Clinical Studies (14)]*. Trough plasma concentrations were approximately 13.3% higher with no increased risk of bleeding seen.

Quinidine:
Study 1: Dabigatran etexilate was given 1 hour after a single oral dose of 600 mg quinidine sulfate. Dabigatran AUC and C_{max} were increased by approximately 100% in an inter-individual group comparison. Subjects experienced adverse events and the study was prematurely terminated.

Study 2: Quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was given over 3 consecutive days, the last evening dose on day 3 with or without quinidine pre-dosing. Dabigatran AUC and C_{max} were increased on average by 53% and 56%, respectively with concomitant quinidine.

Clopidogrel:
When dabigatran etexilate was given concomitantly with a loading dose of 300 mg or 600 mg clopidogrel, the dabigatran AUC and C_{max} increased by approximately 30% to 40% respectively. The concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. The coagulation measures for dabigatran effect, aPTT, ECT or TT, or the inhibition of platelet aggregation (IPA) as measurements of clopidogrel effect remained unchanged when comparing combined treatment and the respective mono-treatments.

Rifampicin:
Pre-dosing of rifampicin at a dose of 600 mg QD for 7 days decreased dabigatran AUC and C_{max} by 66% and 67%, respectively. The effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days *[see Warnings and Precautions (5.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in male and female mice and rats given oral doses of dabigatran etexilate of 30, 100, and 200 mg/kg/day. In both studies, there was no evidence for a carcinogenic potential of dabigatran etexilate.

Dabigatran was not mutagenic in *in vitro* tests, including Ames test and mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* rat bone marrow micronucleus assay.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating (max. 20 days), up to scheduled termination (approximately 7 weeks total) and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male and female fertility were observed at 200 mg/kg (approximately 11 to 14 times human exposure at the MRHD of 220 mg/day based on AUC comparisons). At 200 mg/kg, the number of implantations in females was decreased (approximately 11 to 14 times human exposure at the MRHD based on AUC comparison).

13.2 Animal Toxicology and/or Pharmacology

Acute oral toxicity studies were conducted in rats and mice. In both species, the approximate lethal dose after single oral administration was above 2000 mg/kg. In dogs and Rhesus monkeys, single oral administration of 600 mg/kg dabigatran etexilate did not induce any toxicologically meaningful changes.

In repeat-dose toxicity studies over a maximum of 26 weeks in rats and 52 weeks in Rhesus monkeys, dosages up to 300 mg/kg (free base equivalent) were used. Generally, these doses were well tolerated by both rats and Rhesus monkeys. Bleeding problems were observed in association with trauma (e.g., blood sampling) within the first 4 to 6 hours after administration and are directly related to the pharmacodynamic activity of dabigatran.

In vivo and *ex vivo* animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

14 CLINICAL STUDIES

The clinical evidence for the efficacy of PRADAXA is derived from the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study comparing two blinded doses of PRADAXA (110 mg BID and 150 mg BID) with open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The primary objective in this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The population had approximately equal proportions of patients with $CHADS_2$ score 1, 2 and >3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment exposure of 20 months with PRADAXA given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

2. Previous stroke, transient ischemic attack, or systemic embolism
3. Left ventricular ejection fraction <40%
4. Symptomatic heart failure, ≥NYHA Class 2
5. Age ≥75 years
6. Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

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The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. Fifty percent of the patient population was VKA naïve defined as less than 2 months total life time exposure. Thirty-two percent of the population had never been exposed to a VKA. For those patients randomized to warfarin, the median time in therapeutic range (INR 2 to 3) for the trial was 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), aspirin+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

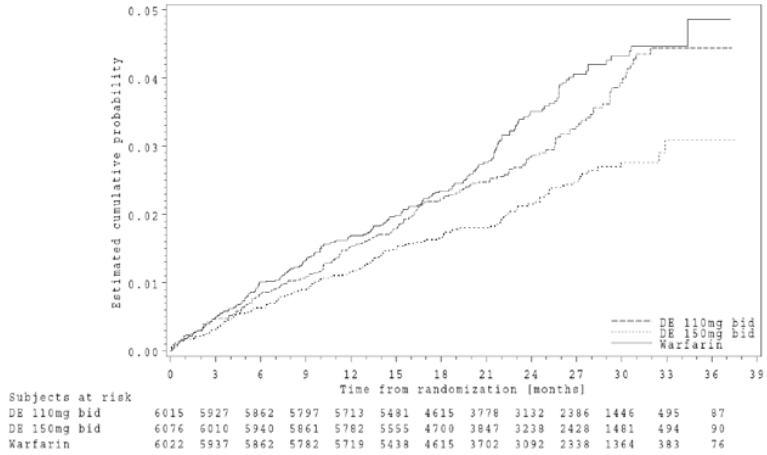
For the primary endpoint, stroke and systemic embolism, no subgroups (i.e., age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin. PRADAXA110 mg was non-inferior to warfarin and PRADAXA150 mg was superior to warfarin in reducing the risk of stroke and/or SEE.

Table 6 First Occurrence of Stroke or Systemic Embolism (Primary Endpoint) in the RE-LY Study

	PRADAXA 110 mg BID	**PRADAXA150 mg BID**	**Warfarin***
Subjects randomized	6015	6076	6022
Stroke and/or SEE			
Incidences (%)	183 (1.54)	134 (1.11)	202 (1.71)
Hazard ratio vs warfarin (95% CI)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	
p value for superiority	p =0.2943	p =0.0001	

% refers to yearly event rate
*dosed to target INR of 2 to 3

Figure 2: Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



The contribution of the components of the composite endpoint, including categories of stroke, is outlined in Table 7. For the individual components of the primary endpoint stroke, ischemic stroke, and hemorrhagic stroke, PRADAXA 150 mg BID was superior to warfarin. PRADAXA 110 mg was comparable to warfarin for the endpoints of stroke and ischemic stroke and superior to warfarin for hemorrhagic stroke.

Table 7 First Occurrence of Ischemic or Hemorrhagic Strokes in the RE-LY Study

	PRADAXA 110 mg BID	**PRADAXA 150 mg BID**	**Warfarin**
Subjects randomized	6015	6076	6022
Stroke			
Incidence (%)	171 (1.44)	122 (1.01)	186 (1.58)
Hazard ratio vs warfarin (95% CI)	0.91 (0.74, 1.12)	0.64 (0.51, 0.81)	
p-value	0.3828	0.0001	
SEE			
Incidence (%)	15 (0.13)	13 (0.11)	21 (0.18)
Hazard ratio vs warfarin (95% CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
Ischemic stroke			
Incidence (%)	152 (1.28)	103 (0.86)	134 (1.14)
Hazard ratio vs warfarin (95% CI)	1.13 (0.89, 1.42)	0.75 (0.58, 0.97)	
p-value	0.3139	0.0296	
Hemorrhagic stroke			
Incidence (%)	14 (0.12)	12 (0.10)	45 (0.38)
Hazard ratio vs warfarin (95% CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	<0.001	<0.001	

% refers to yearly event rate

Both PRADAXA doses reduced all-cause mortality and vascular mortality and the reductions associated with 150 mg were statistically superior to warfarin for vascular death (Table 8).

Table 8 Mortality in the RE-LY Study

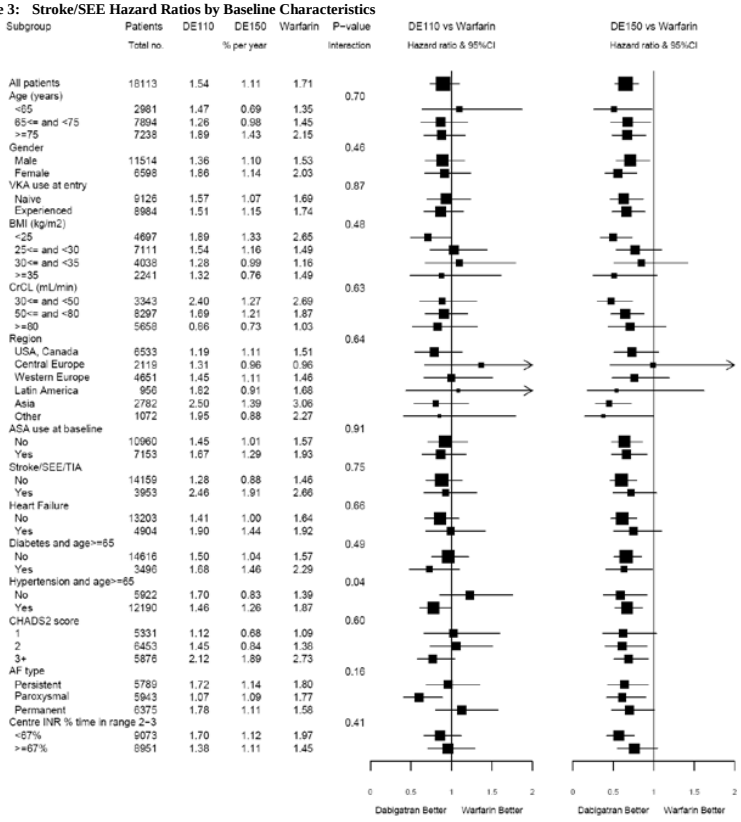
	PRADAXA 110 mg BID	**PRADAXA 150 mg BID**	**Warfarin**
Subjects randomized	6015	6076	6022
All-cause mortality			
Incidence (%)	446 (3.75)	438 (3.64)	487 (4.13)

Hazard ratio vs warfarin (95% CI)	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
Vascular mortality			
Incidence (%)	289 (2.43)	274 (2.28)	317 (2.69)
Hazard ratio vs warfarin (95% CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2081	0.0430	

% refers to yearly event rate

The efficacy of dabigatran 110 mg and 150 mg BID was consistent across all major subgroups (Figure 3). There were too few African-American and Hispanic subjects to adequately assess differences in effects in those populations.

Figure 3: Stroke/SEE Hazard Ratios by Baseline Characteristics



The net clinical benefit as measured by the composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction (MI), all cause deaths, and major bleeds was assessed and is presented as part of Table 9. The yearly event rates for the PRADAXA groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the PRADAXA 110 mg BID and 150 mg BID treatment groups. The absolute risk of MI (including silent MI) was low (0.83% to 0.81%/year) but was greater on PRADAXA (relative risk 1.29 for PRADAXA 110 mg vs warfarin and 1.27 for PRADAXA 150 mg vs warfarin). Other components evaluated included all hospitalizations which had statistically significant fewer hospitalizations at PRADAXA 110 mg BID compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 9 Other Measures Evaluated

	PRADAXA 110 mg BID	**PRADAXA 150 mg BID**	**Warfarin**
Subjects randomized	6015	6076	6022
Stroke/SEE/death			
Incidence (%)	577 (4.85)	520 (4.32)	613 (5.20)
Hazard ratio vs Warfarin (95% CI)	0.93 (0.83, 1.04)	0.83 (0.74. 0.93)	
p-value	0.2206	0.0015	
Stroke/SEE/PE/MI/death/major bleed (net clinical benefit)			
Incidence (%)	863 (7.25)	848 (7.05)	925 (7.84)
Hazard ratio vs Warfarin (95% CI)	0.92 (0.84, 1.01)	0.90 (0.82, 0.99)	
p-value	0.0852	0.0254	
Pulmonary embolism			
Incidence (%)	14 (0.12)	18 (0.15)	12 (0.10)
Hazard ratio vs Warfarin (95% CI)	1.16 (0.54, 2.51)	1.47 (0.71, 3.06)	
p-value	0.7076	0.2980	
Myocardial infarction*			
Incidence (%)	98 (0.82)	97 (0.81)	75 (0.64)
Hazard ratio vs Warfarin (95% CI)	1.29 (0.96, 1.75)	1.27 (0.94, 1.71)	
p-value	0.0929	0.1240	

% refers to yearly event rate
*Myocardial infarction included silent MI

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 110 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a light blue opaque body imprinted with "R110". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0108-54 Unit of use bottle of 60 capsules
- NDC 0597-0108-60 Blister package containing 60 capsules (10 x 6 capsule blister cards) *(hospital unit dose pack)*

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with "R150". The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0135-54 Unit of use bottle of 60 capsules
- NDC 0597-0135-60 Blister package containing 60 capsules (10 x 6 capsule blister cards) *(hospital unit dose pack)*

Storage
Bottles:
Store at 25ºC (77ºF); excursions permitted to 15º-30ºC (59º-86ºF). Once opened, the product must be used within 30 days. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Blisters:
Store at 25ºC (77ºF); excursions permitted to 15º-30ºC (59º-86ºF). Store in the original package in order to protect from moisture.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION
See Medication Guide

17.1 Benefits and Risks

- Summarize the effectiveness and potential side effects of PRADAXA.
- Tell patients to take PRADAXA exactly as prescribed by their health care provider.
- Remind patients not to discontinue PRADAXA without first discussing it with the health care provider who prescribed it.
- Patients should be advised not to chew the capsules before swallowing and not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages).
- Recommend that patients read the Medication Guide.

17.2 Bleeding

Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding.

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17.3 Other Signs and Symptoms Requiring Medical Attention

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or dyspepsia like symptoms:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

17.4 Invasive or Surgical Procedures

Patients should inform their health care provider that they are taking PRADAXA before any invasive procedure is scheduled.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs).

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Ridgefield, CT 06877 USA

Rev: May 2010

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MEDICATION GUIDE

PRADAXA (pra dax' a)
(dabigatran etexilate)
capsules

Please read the Medication Guide that comes with PRADAXA before you start taking it and each time you refill your prescription. There may be new information. This leaflet does not take the place of discussions with your health care provider about your medical condition or your treatment.

Please read this document carefully; many sections contain safety information.

What is the most important information I should know about PRADAXA?
Take PRADAXA exactly as prescribed to lower the risk of blood clots forming in your body. PRADAXA is used to prevent your chance of having a stroke or other serious problems caused by a blood clot in your body. However, there is an increased risk for serious and life-threatening bleeding problems while taking PRADAXA, especially if you have severe kidney illness or are taking certain other medications. You should discuss any history of bleeding problems or condition that increases the risk of bleeding with your health care provider before taking PRADAXA. Please also see "**How should I take PRADAXA?**" for important dosing instructions.

What is PRADAXA?
PRADAXA is a medicine that changes how your blood clots. It is used to lower the risk of blood clots forming in your body. Blood clots can cause a stroke, heart attack, or other serious conditions.

Do not take dabigatran if you have:
- Active major bleeding or medical conditions associated with an increased risk of bleeding
- Severe kidney illness (CrCl <30 mL/min)
- Concomitant treatment with systemic ketoconazole
- Placement of indwelling spinal or epidural catheter or port and within first hour after removal

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You should not take PRADAXA if you are allergic (hypersensitive) to the active ingredient dabigatran etexilate mesylate or any of the other ingredients listed at the end of this leaflet.

Whenever possible you should stop taking PRADAXA at least 2 days before undergoing elective surgery or invasive procedures, or as instructed by the health care provider who prescribed PRADAXA for you.

You may also have a higher risk of bleeding if you take PRADAXA and:
- Regularly take other medicines that increase your risk of bleeding including aspirin and clopidogrel, and non-steroidal anti-inflammatory drugs (NSAIDs)
- Have a condition such as a stomach ulcer or a history of your stomach bleeding
- Have severe kidney illness
- If you are older than 75 years

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Always tell all of your health care providers that you take PRADAXA.

PRADAXA may cause bleeding and bleeding related problems (e.g., anemia), because it changes how your blood clots.

Get emergency care right away if you have any of the following, which may be a sign or symptom of serious bleeding:
- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood or vomit that looks like coffee grounds

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Call your health care provider right away if you have of the following, which may be a sign or symptom of bleeding:
- Pain, swelling, or discomfort in a joint
- Headaches, dizziness, or weakness
- Frequent nose bleeds
- Unusual bleeding from your gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

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Call your health care provider if you experience any signs or symptoms of:

- Stomach burning or stomach upset (dyspepsia)
- Abdominal pain or discomfort
- Epigastric discomfort, GERD

What should I tell my health care provider before taking PRADAXA?

Before taking PRADAXA, tell your health care provider about all your medical conditions, including:

- If you have kidney problems
- If you have a history of bleeding problems
- If you have a history of stomach ulcers
- If you are pregnant or plan to become pregnant. It is not known if dabigatran will harm your unborn baby.
- If you are breast-feeding. It is not known if dabigatran will pass into your breast milk. You and your health care provider should decide if you should take PRADAXA and breast-feed.

Tell your health care provider about all the medicines you take including:

- Any prescription medicines, including, but not limited to, anticoagulant drugs such as Coumadin® (warfarin or vitamin K antagonists), aspirin, clopidogrel, unfractionated heparins (except at doses necessary to maintain a patent central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, prasugrel; and the P-gp inhibitors itraconazole, tacrolimus, cyclosporine; and ritonavir, nelfinavir, saquinavir and tipranavir, and any non-prescription medicines, including vitamins, and herbal supplements.
- Know the medicines you take. Keep a list of them and show it to your health care provider and pharmacist when you get a new medicine or any time you visit the health care provider or pick up a prescription.
- Tell your health care provider if you are allergic to any medicines.
- Tell your health care provider about all medicines you are taking, including all prescription and over-the-counter (OTC) medicines, vitamins, and herbal supplements. Some of your other medicines or herbal supplements may affect the way PRADAXA works.

How should I take PRADAXA?

- Follow your health care provider's directions carefully and this medication guide.
- Do not take PRADAXA more often than prescribed.
- Do not stop taking PRADAXA without first talking with your health care provider.
- PRADAXA is to be taken by mouth, twice daily, with or without food.
- Do not open the capsules. The little pellets inside the capsule should not be emptied from the capsule. Do not swallow the pellets outside the capsule.
- Do not take 2 doses of PRADAXA at one time to make up for a missed dose. If you forget to take your prescribed dose of PRADAXA at your scheduled time, take the dose as soon as possible. A dose may be taken up to 6 hours prior to the next scheduled dose. A missed dose should be skipped if it cannot be taken more than 6 hours before the next scheduled dose.
- If you take more PRADAXA capsules than prescribed, go to the nearest hospital emergency room, call your health care provider or Poison Control Center.
- If you are having surgeries, medical or dental procedures, your PRADAXA may have to be stopped for a short time.

What should I avoid while taking PRADAXA?

- Do not start, stop, or change any medicine without first talking with your health care provider.
- Avoid activities or sports that may cause a serious injury.
- Call your health care provider right away if you fall or injure yourself, especially if you hit your head. Your health care provider may need to check you.

What are possible side effects of PRADAXA?

Bleeding and bleeding related events (e.g., anemia) may be caused by taking PRADAXA. Major or severe bleeding may occur and may lead to hospitalization or death. Other possible side effects may include: stomach pain or burning or abdominal pain; difficulty breathing; dizziness or lightheadedness; swelling in your hands, feet or face; feeling tired; diarrhea; chest pain or pressure in your chest; pain in your joints or your joints hurting; cough; runny nose or irritated throat. This is not a complete list of side effects and should not take the place of discussions with your health care provider. Your health care provider or pharmacist can give you more information about the possible side effects of this drug. Please speak to your health care provider if you have questions about any side effects that you think may be related to PRADAXA.

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Tell your health care provider if you have any side effect that bothers you or that does not go away.

Call your health care provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088, or by visiting www.fda.gov/medwatch.

What important safety information should I know about PRADAXA?

Please read this document carefully; many sections contain safety information.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PRADAXA for a condition for which it was not prescribed. Do not give your PRADAXA to other people, even if they have similar symptoms. It may hurt them.

How do I store PRADAXA?

Store PRADAXA at Room Temperature [77°F (25°C)]. Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Store the capsules in the original package in order to protect from moisture.

Keep out of the reach of children.

Other information about PRADAXA.

This Medication Guide summarizes the most important information about PRADAXA. If you would like more information, talk with your health care provider. You can ask your pharmacist or health care provider for information about PRADAXA that is written for health professionals. For more information, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in PRADAXA?
Active ingredient: dabigatran etexilate mesylate

Inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shells are composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink.

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This Medication Guide has been approved by the US Food and Drug Administration.